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Editorial

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## Link not proven

Two events within the past year have highlighted the question of the possible lasting cerebral effects of repeated severe hypoglycaemia in people with insulin dependent diabetes mellitus. Firstly, in August 1995, the British Diabetic Association specifically requested research proposals on the cognitive effects of diabetes after their working party on cognitive impairment identified repeated severe hypoglycaemia as one possible cause of (mostly) mild cognitive decrements in some people with insulin dependent diabetes mellitus (unpublished data). Secondly, the diabetes control and complications trial has reported no untoward neuropsychological effects of severe

hypoglycaemia in patients with insulin dependent diabetes.[1]

The human brain accounts for about 20% of the body's metabolic consumption and is obliged to use glucose exclusively as its fuel. Therefore, when it is temporarily starved of glucose, brain functions suffer: thinking processes are impaired and a tense, tired mood state ensues. If profound neuroglycopenia continues untreated the result may be coma, seizure, and (rarely) severe brain damage. Hypoglycaemia is associated with significant morbidity and accounts for about 1-2% of deaths among diabetic patients,[2] although this is still much lower than the mortality from diabetic ketoacidosis (6%). The severity of hypoglycaemia is defined by individuals' ability to treat themselves: severe episodes are those that require help from a third party to effect recovery. For people with insulin dependent diabetes, hypoglycaemia is the most feared side effect of treatment. Because episodes of severe hypoglycaemia can involve relatively prolonged neuroglycopenia, concern has arisen about their long term effects on brain function. Increasingly, patients, their carers, and diabetes researchers are asking whether repeated severe hypoglycaemia causes lasting cognitive decrements. How should we answer?

There is evidence that repeated severe hypoglycaemia in young children, especially those with very early onset of diabetes, contributes to slowed mental development and may reduce eventual IQ level.[3] In adults there is less agreement about the cerebral effects of severe hypoglycaemia. A prolonged, single episode of severe hypoglycaemia may cause lasting cognitive deficits, but this is uncommon. Where episodes of hypoglycaemia are unusually frequent and severe, and where there are other predisposing factors, mental abilities and personality may be affected.[4]

Four cross sectional studies, which used retrospective reports of severe hypoglycaemia, have obtained results consistent with the hypothesis that, on average, mild cognitive decrement may follow multiple episodes of severe hypoglycaemia. In two small studies, adults with insulin dependent diabetes who had histories of repeated severe hypoglycaemia scored lower on some neuropsychological tests than matched groups of diabetic patients who had never experienced severe hypoglycaemia.[5] [6] However, both studies used several cognitive measures, with no corrections for multiple statistical testing, and did not always concur on the cognitive domains that distinguished patients with and without a history of severe hypoglycaemia. Findings from a cohort of 100 people with insulin treated diabetes tested by our research group suggested a modest association

between the reported frequency of severe hypoglycaemia and estimated IQ decrement, lower levels of current IQ, and slowed and more variable reaction times.[7 8 9] An independent research team has replicated this finding in a group of 70 patients.[10] Projecting from these results, an otherwise healthy diabetic adult experiencing five or more episodes of severe hypoglycaemia might expect a modest decrement of about 5-6 IQ points. Criticism of inaccurate ascertainment of severe hypoglycaemia by retrospective methods is appropriate, but it is not apparent how this limitation might have produced a spurious positive result (type I statistical error). The possibility that people with lower IQs might be prone to more episodes of severe hypoglycaemia (the reverse hypothesis of the one suggested above) is partly refuted by the fact that the frequency of severe hypoglycaemia correlated significantly with current IQ level but not with estimated premorbid IQ.[7]

By contrast, two longitudinal studies have failed to find any deleterious cognitive effects of repeated severe hypoglycaemia in adults with insulin dependent diabetes. In a 7.5 year follow up of the Stockholm diabetes intervention study, no cognitive differences were found between groups of diabetic patients subjected to intensive or to conventional insulin therapy, despite the former group experiencing significantly more severe hypoglycaemia.[11] There are several reasons, none particularly compelling, why this study might have produced an “unsafe” null result, including inefficient separation of the groups based on patients' experience of hypoglycaemia, the use of a brief and quirky neuropsychological test battery, insufficient duration of follow up, and insufficient statistical power. However, the study's null result is supported by the recent findings of the diabetes control and complications trial.[1]

This group's multicentre randomised controlled trial compared intensified (n = 711) versus conventional (n = 730) insulin therapy in young people with insulin dependent diabetes.[1] Its 1441 participants, recruited from 29 centres, were aged 13-39 years on entry to the trial and were studied prospectively for an average of 6.5 years. The study yielded a total of 9300 years of patient observation. Information was obtained on hypoglycaemic events, which were reported to the trial's coordinating centre as soon as possible after their occurrence. An extensive and sensitive neuropsychological test battery, covering eight cognitive domains, was administered at two, five, and seven years. Attrition was minimal; for example, 98% of the expected neuropsychological test sessions were completed. General linear regression and analysis of covariance were used to examine the effects of

hypoglycaemia on cognitive domains. No evidence was found to link experience of severe hypoglycaemia with cognitive decrements. However, it should be noted that the participants were young (mean age 27 years), had relatively short duration of disease (5.5 years), had a high mean intellectual ability, were followed up for a relatively short period of time on average, had little or no exposure to severe hypoglycaemia before the study, and that only 23 of them had experienced more than five episodes of hypoglycaemic coma or seizure during the trial. The grouping of mental test results into eight cognitive domains, none of which is directly comparable to performance and general IQ, was not validated by factor analysis. Moreover, any changes in cognitive function across time that might or might not be linked to severe hypoglycaemia must be separated, not only from the usual practice effects but from the effects of cognitive development, since some subjects were as young as 13 years on entry to the study. Any or all of these factors might have contributed to a null result from which it would not be safe to generalise to the wider diabetic population. Neither of the longitudinal trials has had a sufficiently long follow up to allow any cognitive decrement to emerge.

In the light of the published research, we are inclined to return the uniquely Scottish legal verdict of “not proven” regarding this controversial issue. However, we can at least state that, among young adults with insulin dependent diabetes, the average cerebral impact of several episodes of severe hypoglycaemia over a period of between five and 15 years is either mild or negligible. For a few individuals, with vulnerability factors which as yet remain obscure, brain function may be permanently and importantly affected. Strict glycaemic control has the great benefit of reducing target organ damage—delaying the onset and slowing the progress of retinopathy, nephropathy, and neuropathy—but brings with it a threefold increase in severe hypoglycaemia.[12] No one doubts that severe hypoglycaemia should be avoided, but patients and their carers are right in demanding more research to help them make intelligent decisions about the long term trade off between the Scylla of hyperglycaemia and the possible Charybdis of hypoglycaemia.

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